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Requester's Full Name: Chen, Chanshwa Examiner #: 79773 Date: 12/13/2002

Art Unit: 1641 Phone Number 30[illegible]4086 Serial Number: 09/695,919

Mail Box and Bldg/Room Location: 8D28 Results Format Preferred (circle): PAPER DISK E-MAIL

7E12

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): Please See attached

Earliest Priority Filing Date: 10/27/1999

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please disregard claim #5

Point of Contact:
Mona Smith
Technical Information Specialist
CM1 6A01
Tel: 308-3278

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: M. SMITH	NA Sequence (#)		STN	
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)		Questel/Orbit	
Date Searcher Picked Up: 12/15/02	Bibliographic	X	Dr.Link	
Date Completed: 1/10/03	Litigation		Lexis/Nexis	
Searcher Prep & Review Time: 60	Fulltext		Sequence Systems	
Clerical Prep Time:	Patent Family		WWW/Internet	
Online Time: 60	Other		Other (specify)	

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FILE COVERS 1907 - 10 Jan 2003  VOL 138 ISS 3
FILE LAST UPDATED: 9 Jan 2003  (20030109/ED)

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check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> d stat que
L1          6394 SEA FILE=REGISTRY INSULIN/BI
L2             1 SEA FILE=REGISTRY C-PEPTIDE/CN
L3           101 SEA FILE=REGISTRY PREPROINSULIN/BI
L5        153367 SEA FILE=HCAPLUS L1 OR INSULIN?
L6          4009 SEA FILE=HCAPLUS L2 OR C(W)PEPTIDE?
L7           542 SEA FILE=HCAPLUS L3 OR PREPROINSULIN?
L9             3 SEA FILE=HCAPLUS (L6 OR L7) (L)IMPUR?
L10            2 SEA FILE=HCAPLUS L9 (L)L5
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10/7/99

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=> d ibib abs hitrn l10 1-2

L10  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2001:320215  HCAPLUS
DOCUMENT NUMBER:          134:339540
TITLE:                    A new immunologic assay to determine C-
                          peptide containing impurities in
                          samples of human insulin and derivatives
                          thereof
INVENTOR(S):              Gerl, Martin; Steinert, Cornelia
PATENT ASSIGNEE(S):       Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE:                   PCT Int. Appl., 51 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
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Application

Searched by M. Smith

WO 2001031336 A2 20010503 WO 2000-EP10482 20001025
WO 2001031336 A3 20011108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1228374 A2 20020807 EP 2000-974449 20001025
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
PRIORITY APPLN. INFO.: DE 1999-19951684 A 19991027
WO 2000-EP10482 W 20001025

AB The invention relates to a process for detecting or detg. a **C-peptide**-contg. **impurity** in a sample of recombinantly produced human **insulin** or a deriv. thereof, by a non-radioactive assay, comprising the steps: (a) prepg. a sample of recombinantly produced human **insulin** or a deriv. thereof; (b) mixing the samples with diln. buffer; (c) adding a tracer to mixt. (b); (d) adding antibody specific for the **C-peptide impurity** to mixt. (c); (e) adding "**C-peptide** second antibody bead" having at least one label to mixt. (d); and (f) detecting or detg. the presence of the **C-peptide**-contg. **impurity**.

IT **59112-80-0, C-Peptide**
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); ARU (Analytical role, unclassified); BOC (Biological occurrence); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence)
(anti-**C-peptide** antibodies for fluorescent immunoassay of **C-peptide** contg. **impurities** in recombinant human **insulin** and derivs.)

IT **9004-10-8P, Insulin**, biological studies
RL: AMX (Analytical matrix); BPN (Biosynthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(anti-**C-peptide** antibodies for fluorescent immunoassay of **C-peptide** contg. **impurities** in recombinant human **insulin** and derivs.)

L10 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1973:476289 HCAPLUS
DOCUMENT NUMBER: 79:76289
TITLE: Conversion of proinsulin to insulin. III. Studies in-vitro with a crude secretion granule fraction isolated from rat islets of Langerhans
AUTHOR(S): Kemmler, Wolfgang; Steiner, Donald F.; Borg, Jo
CORPORATE SOURCE: Pritzker Sch. Med., Univ. Chicago, Chicago, IL, USA
SOURCE: Journal of Biological Chemistry (1973), 248(13), 4544-51
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Proinsulin is converted to **insulin** in an **impure** secretion granule fraction prepd. from rat islets of Langerhans that have been labeled before homogenization with leucine-3H or arginine-3H. During incubation of this particulate fraction at pH 6.3 and 37.degree., the

initial rate of conversion of the endogenous labeled proinsulin was similar to that obsd. in whole islets, while externally added labeled proinsulin was not cleaved. Only intact granules catalyzed conversion, and thus the pH optimum of .apprx.6.0 for this process corresponded closely to that for granule stability. The most rapid in vitro cleavage of endogenous proinsulin was obsd. when the islets were prelabeled with leucine-3H for 30 min, followed by a 15-min chase to allow time for the transport of newly synthesized proinsulin to the Golgi apparatus and new secretory granules. Several proteinase inhibitors, including soybean trypsin inhibitor, pancreatic trypsin inhibitor, diisopropyl fluorophosphate, N-.alpha.-p-tosyl-L-lysine chloromethyl ketone.HCl, benzamidine, p-nitrophenyl-p'-guanidinobenzoate-HCl, N-ethylmaleimide, and iodoacetate, did not inhibit the conversion in vitro, possibly due to a lack of permeability of the granules to some of these substances; high concns. of p-chloromercuribenzoate completely inhibited the conversion. The products of in vitro conversion were characterized by polyacrylamide gel and thin-layer electrophoresis as rat **insulins** I and II and their corresponding **C-peptides**. The residual proinsulin fraction after incubation consisted mainly of partly cleaved intermediate forms. When islets were pre-labeled with arginine-3H before prepn. of the granule fraction, in vitro conversion was accompanied by the release from the cleavage regions of free arginine rather than dipeptides of arginine or lysylarginine. Granule prepns. disrupted by repeated freeze-thawing lost their ability to introduce cleavages in intact proinsulin but were still able to rapidly remove COOH-terminal arginine residues from lightly trypsinized proinsulin. A low level of tryptic-like activity, as indicated by the slow cleavage of N-.alpha.-tosyl-L-[methyl-3H]arginine methyl ester, can still be detected in the disrupted prepns. These results are in accord with the hypothesis that enzyme(s) having trypsin-like and carboxypeptidase B-like activity exist in the secretory granules of the .beta.-cells and participate in the conversion of proinsulin to **insulin**.

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=> d stat que
L1          6394 SEA FILE=REGISTRY INSULIN/BI
L2             1 SEA FILE=REGISTRY C-PEPTIDE/CN
L3           101 SEA FILE=REGISTRY PREPROINSULIN/BI
L4          2041 SEA FILE=REGISTRY ANTIBODIES/BI OR ANTIBODY/BI
L5        153367 SEA FILE=HCAPLUS L1 OR INSULIN?
L6          4009 SEA FILE=HCAPLUS L2 OR C(W)PEPTIDE?
L7           542 SEA FILE=HCAPLUS L3 OR PREPROINSULIN?
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L9             3 SEA FILE=HCAPLUS (L6 OR L7) (L)IMPUR?
L10            2 SEA FILE=HCAPLUS L9 (L)L5
L11         4587 SEA FILE=HCAPLUS (L5) AND (ASSAY? OR ANALY? OR EXAMIN? OR
                 EVAL? OR TEST?) AND L8
L12          235 SEA FILE=HCAPLUS L11 (L)(L6 OR L7)
L13           12 SEA FILE=HCAPLUS MONKEY(5A)L6
L14            1 SEA FILE=HCAPLUS L12(L)L13
L15            0 SEA FILE=HCAPLUS L14 NOT L10
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Searched by M. Smith

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L1          6394 SEA FILE=REGISTRY INSULIN/BI
L2             1 SEA FILE=REGISTRY C-PEPTIDE/CN
L3           101 SEA FILE=REGISTRY PREPROINSULIN/BI
L5        153367 SEA FILE=HCAPLUS L1 OR INSULIN?
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L7           542 SEA FILE=HCAPLUS L3 OR PREPROINSULIN?
L9             3 SEA FILE=HCAPLUS (L6 OR L7) (L)IMPUR?
L10            2 SEA FILE=HCAPLUS L9 (L)L5
L16            1 SEA FILE=HCAPLUS L9 NOT L10


=> d ibib abs hitrn l16

L16  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         1987:476681  HCAPLUS
DOCUMENT NUMBER:          107:76681
TITLE:                    Effect of a purified amylase inhibitor on carbohydrate
                          metabolism after a mixed meal in healthy humans
AUTHOR(S):                Boivin, Michel; Zinsmeister, Alan R.; Go, Vay L. W.;
                          DiMagno, Eugene P.
CORPORATE SOURCE:         Mayo Grad. Sch. Med., Rochester, MN, 55905, USA
SOURCE:                   Mayo Clinic Proceedings (1987), 62(4), 249-55
                          CODEN: MACPAJ; ISSN: 0025-6196
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Eight healthy subjects were randomized to receive 2.0 or 2.9 g of amylase
     inhibitor with a 650-cal meal that contained carbohydrate, fat, and
     protein.  In comparison with a placebo, ingestion of 2.9 g, but not 2.0 g,
     of the inhibitor significantly reduced postprandial increases in plasma
     glucose, C peptide, and gastric inhibitory
     polypeptide.  Similarly, 2.9 g of the inhibitor in comparison with 2.0 g
     was assocd. with more carbohydrate malabsorption and more breath H2
     excretion.  Because the carbohdrate malabsorption obsd. with the 2.9-g
     dose was similar to that with the previously tested 5- and 10-g doses of
     the inhibitor but diarrhea was less frequent, impurities in the
     partially purified prepn. may, in part, have been responsible for these
     adverse effects.  Therefore, this dose is appropriate for ue in studies to
     det. whether the inhibitor has a beneficial effect in patients with
     diabetes mellitus or obesity.
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         (c) 2003 IFI/CLAIMS(R)
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         (c) 2002 Thomson Derwent
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         (c) 2003 EPO
File 351:Derwent WPI 1963-2002/UD,UM &UP=200301
         (c) 2003  Thomson Derwent
File 357:Derwent Biotech Res. _1982-2002/Dec W5
         (c) 2002 Thomson Derwent & ISI
File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 1998 Inst for Sci Info
File 440:Current Contents Search(R) 1990-2003/Jan 10
         (c) 2003 Inst for Sci Info
?ds

Set     Items   Description
S1      25619   (C(W)PEPTIDE? OR C(W)PROTEIN? OR PREPROINSULIN?) (S) INSUL-
             IN?
S2          9   S1 AND IMPUR?
S3          9   RD (unique items)
?t3/3 ab/1-9
>>>No matching display code(s) found in file(s): 342, 345

 3/AB/1     (Item 1 from file: 70)
DIALOG(R)File  70:SEDBASE
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00590751  SEDBASE No.: 00271827   Line Count: 133
Number of Cited Reference: 14
Drug Name: INSULIN HUMAN
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Drug Classification: 44.01
Effect Interaction Name: HYPOGLYCEMIA
Effect Classification Code: 06.03
Synonym(s) for Effect Name: GLUCOSE METABOLISM DISTURBANCE; HYPOGLYKEMIA

FACTORS OF INFLUENCE: DEVIATION FROM ROUTINE; CONTINUOUS SUBCUTANEOUS INSULIN INFUSION
Source: Side Effects of Drugs Annual-13,381 Side Effects of Drugs Annual-12,358 Side Effects of Drugs Annual-14,372

EMBASE Abstract: The case-histories of 3 patients with insulin-dependent diabetes mellitus (IDDM) suggested that, after a switch from beef/porcine to human insulin, a given level of hypoglycaemia may cause less pronounced sympathoadrenal symptoms (tremor, sweating, &c), so that there is less warning of impending unconsciousness. This possibility was investigated by questioning of 176 IDDM patients who had switched from beef/porcine to human insulin with negligible change in dosage 1-48 months earlier. 66 (36%) said that their symptoms of hypoglycaemia had changed from those of sympathoadrenal activation to those of neuroglycopenia. This disadvantage of human insulin is an argument for continued availability of beef/porcine insulin.

EMBASE Abstract: The incidence of severed hypoglycemia was determined in a 1-yr prospective study of 350 insulin-dependent diabetic (IDDM) children. There were no significant differences in mean glycosylated hemoglobin, age, and duration of disease between the patients who had severe hypoglycemia and those who did not. There were 25 episodes in 24 patients (6.8%). Their insulin doses at the time of the episode (U midline dot kg-1 midline dot day-1) were significantly higher than those of the nonhypoglycemic group (mean plus-or-minus sign SD 1.01 plus-or-minus sign 0.30 vs 0.89 plus-or-minus sign 0.29; P = 0.4). The hypoglycemic group had a significantly higher mean number of previous episodes of severe hypoglycemia than the nonhypoglycemic group (0.92 plus-or-minus sign 1.18 vs. 0.25 plus-or-minus sign 0.68; P = .01). In only 64% of the episodes, an unusual circumstance such as strenuous physical activity or missed or delayed meals preceded the event. Multivariate analysis of the data by logistic regression showed risks of developing hypoglycemia of 2.5 per 0.5 U/day insulin and of 2.0 per previous episode of severe hypoglycemia. We conclude that severe hypoglycemia may be a recurrent problem in some diabetic children, but it does not appear to be related to age or blood glucose control. The presence of previous episodes may be a guide to identify patients at greater risk of developing severe hypoglycemia. Adherence to regular testing, strict spacing and consistency of meals, and extra food for extra activity may reduce this serious complication.

EMBASE Abstract: The frequency of nocturnal hypoglycaemia, i.e. blood glucose concentration (BG) < 3.0 mmol/l, was evaluated in consecutively selected insulin-dependent patients on multiple insulin injections (MII), n = 23, of continuous subcutaneous insulin infusions (CSII), n = 25. Blood was sampled hourly from 23.00 to 07.00. Seven patients (30%) on MII had at least one BG < 3.0 mmol/l during the night. Eleven patients (44%) on CSII had hypoglycaemia (NS). The total number of BGs < 3.0 mmol/l was higher on CSII, 42 of 225, versus 16 of 207 on MII (p < 0.025). The duration of hypoglycaemia was 2 hours (range 1-6) on MII and 4 hours (range 1-7) on CSII with a maximal prevalence at 4 hours and between 5 and 7 hours, respectively (p = < 0.05). The frequency of nocturnal hypoglycaemia is high in patients on intensified insulin regimens. Nocturnal hypoglycaemia occurs later in the night and is of longer duration on CSII than on MII. HbA(1c), BG before bedtime and in the morning might be useful in the evaluation of nocturnal hypoglycaemia.

EMBASE Abstract: To assess the effect of asymptomatic nocturnal hypoglycemia on glycemic control in insulin-dependent diabetes mellitus, we

studied, on three nights, 10 patients receiving their usual regimens of continuous subcutaneous insulin infusion. During a control night, the patients' mean (plus-or-minus sign SE) plasma glucose level reached a nadir of 4.5 plus-or-minus sign 0.2 mmol per liter at 3 a.m. ; the fasting glucose level was 5.9 plus-or-minus sign 0.3 mmol per liter at 7:30 a.m., and a peak glucose level of 8.6 plus-or-minus sign 0.3 mmol per liter was reached at 10 a.m., after breakfast. During nights two and three, supplemental insulin was infused intravenously from 10 p.m. to 2 a.m. to simulate a clinical overdose of insulin. On these nights, either hypoglycemia (2.4 plus-or-minus sign 0.2 mmol per liter) was permitted to occur or a nearly normal glucose level (5.5 mmol per liter) was maintained by infusion of glucose. The subjects were asymptomatic on all three nights. Despite comparable plasma free insulin levels from 4 to 11 a.m., both fasting (7.3 plus-or-minus sign 0.2 mmol per liter) and postbreakfast (12.5 plus-or-minus sign 0.4 mmol per liter) plasma glucose levels were significantly higher after hypoglycemia than when hypoglycemia was prevented (6.2 plus-or- minus sign 0.2 mmol per liter and 8.7 plus-or-minus sign 0.4 mmol per liter, respectively; $P < 0.001$ in both cases). Fasting levels of plasma glucose correlated directly with overnight plasma levels of epinephrine ($r = 0.78$, $P < 0.001$), growth hormone ($r = 0.57$, $P < 0.009$), and cortisol ($r = 0.52$, $P < 0.02$) but correlated inversely with the overnight nadit of plasma glucose ($r = -0.62$, $P < 0.005$). We conclude that asymptomatic nocturnal hypoglycemia can cause clinically important deterioration in glycemic control (the Somogyi phenomenon) in patients receiving intensive insulin therapy, and should therefore be considered in the differential diagnosis of unexplained morning hyperglycemia.

EMBASE Abstract: Sixty-six patients with secondary failure to oral hypoglycaemic therapy were assessed in hospital, and those whose fasting blood glucose concentration was greater than or equal 10.0 mmol l-1 were treated with insulin once a day for 6 months. Only 22 patients fulfilled this criterion and they were randomly allocated to a daily injection of either Humulin-Zn (12 patients) or Neulente insulin (10 patients). The remaining patients were considered to be noncompliant with therapy. At the end of 6 months insulin therapy a significant ($p < 0.05$) improvement

EMBASE Abstract: The main aspects of insulin therapy in elderly type 2 diabetics are the following. (1) So-called asymptomatic hyperglycemia (fasting blood glucose concentrations exceeding 8 mmol/l) in elderly patients is often associated with reduced wellbeing and a trial of insulin therapy should be given. (2) The need for this type of therapy has to be re-evaluated from time to time. C - peptide values can help to distinguish between diet failure and beta-cell failure. (3) The insulin requirement can be very small and even small doses may have to be split into two daily injections. (4) To detect over- insulinization regular blood glucose measurements at different times are indispensable.

Side Effects of Drugs Annual-13,381 Side Effects of Drugs Annual-12,358 Side Effects of Drugs Annual-14,372

3/AB/2 (Item 2 from file: 70)
DIALOG(R)File 70:SEDBASE

00590750 SEDBASE No.: 00271810 Line Count: 133
Number of Cited Reference: 14
Drug Name: INSULIN

Drug Classification: 44.01
Effect Interaction Name: HYPOGLYCEMIA
Effect Classification Code: 06.03

Searched by M. Smith

Synonym(s) for Effect Name: GLUCOSE METABOLISM DISTURBANCE; HYPOGLYKEMIA

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of 4.5 plus-or-minus sign 0.2 mmol per liter at 3 a.m. ; the fasting glucose level was 5.9 plus-or-minus sign 0.3 mmol per liter at 7:30 a.m., and a peak glucose level of 8.6 plus-or-minus sign 0.3 mmol per liter was reached at 10 a.m., after breakfast. During nights two and three, supplemental insulin was infused intravenously from 10 p.m. to 2 a.m. to simulate a clinical overdose of insulin. On these nights, either hypoglycemia (2.4 plus-or-minus sign 0.2 mmol per liter) was permitted to occur or a nearly normal glucose level (5.5 mmol per liter) was maintained by infusion of glucose. The subjects were asymptomatic on all three nights. Despite comparable plasma free insulin levels from 4 to 11 a.m., both fasting (7.3 plus-or-minus sign 0.2 mmol per liter) and postbreakfast (12.5 plus-or-minus sign 0.4 mmol per liter) plasma glucose levels were significantly higher after hypoglycemia than when hypoglycemia was prevented (6.2 plus-or- minus sign 0.2 mmol per liter and 8.7 plus-or-minus sign 0.4 mmol per liter, respectively; $P < 0.001$ in both cases). Fasting levels of plasma glucose correlated directly with overnight plasma levels of epinephrine ($r = 0.78$, $P < 0.001$), growth hormone ($r = 0.57$, $P < 0.009$), and cortisol ($r = 0.52$, $P < 0.02$) but correlated inversely with the overnight nadit of plasma glucose ($r = -0.62$, $P < 0.005$). We conclude that asymptomatic nocturnal hypoglycemia can cause clinically important deterioration in glycemic control (the Somogyi phenomenon) in patients receiving intensive insulin therapy, and should therefore be considered in the differential diagnosis of unexplained morning hyperglycemia.

EMBASE Abstract: Sixty-six patients with secondary failure to oral hypoglycaemic therapy were assessed in hospital, and those whose fasting blood glucose concentration was greater than or equal 10.0 mmol l-1 were treated with insulin once a day for 6 months. Only 22 patients fulfilled this criterion and they were randomly allocated to a daily injection of either Humulin-Zn (12 patients) or Neulente insulin (10 patients). The remaining patients were considered to be noncompliant with therapy. At the end of 6 months insulin therapy a significant ($p < 0.05$) improvement

EMBASE Abstract: The main aspects of insulin therapy in elderly type 2 diabetics are the following. (1) So-called asymptomatic hyperglycemia (fasting blood glucose concentrations exceeding 8 mmol/l) in elderly patients is often associated with reduced wellbeing and a trial of insulin therapy should be given. (2) The need for this type of therapy has to be re-evaluated from time to time. C - peptide values can help to distinguish between diet failure and beta-cell failure. (3) The insulin requirement can be very small and even small doses may have to be split into two daily injections. (4) To detect over- insulinization regular blood glucose measurements at different times are indispensable.

Side Effects of Drugs Annual-13,381 Side Effects of Drugs Annual-12,358 Side Effects of Drugs Annual-14,372

3/AB/3 (Item 3 from file: 70)
DIALOG(R)File 70:SEDBASE

00590744 SEDBASE No.: 00271783 Line Count: 104
Number of Cited Reference: 2
Drug Name: INSULIN

Drug Classification: 44.01
Effect Interaction Name: CONSCIOUSNESS LOSS (SYMPTOM OF HYPOGLYCEMIA)
Effect Classification Code: 14.02
Synonym(s) for Effect Name: UNCONSCIOUSNESS
Source: Side Effects of Drugs Annual-13,381 Side Effects of Drugs Annual-14,372

EMBASE Abstract: The case-histories of 3 patients with insulin-dependent diabetes mellitus (IDDM) suggested that, after a switch from beef/porcine to human insulin, a given level of hypoglycaemia may cause less pronounced sympathoadrenal symptoms (tremor, sweating, &c), so that there is less warning of impending unconsciousness. This possibility was investigated by questioning of 176 IDDM patients who had switched from beef/porcine to human insulin with negligible change in dosage 1-48 months earlier. 66 (36%) said that their symptoms of hypoglycaemia had changed from those of sympathoadrenal activation to those of neuroglycopenia. This disadvantage of human insulin is an argument for continued availability of beef/porcine insulin.

EMBASE Abstract: The incidence of severed hypoglycemia was determined in a 1-yr prospective study of 350 insulin-dependent diabetic (IDDM) children. There were no significant differences in mean glycosylated hemoglobin, age, and duration of disease between the patients who had severe hypoglycemia and those who did not. There were 25 episodes in 24 patients (6.8%). Their insulin doses at the time of the episode (U midline dot kg-1 midline dot day-1) were significantly higher than those of the nonhypoglycemic group (mean plus-or-minus sign SD 1.01 plus-or-minus sign 0.30 vs 0.89 plus-or-minus sign 0.29; P = 0.4). The hypoglycemic group had a significantly higher mean number of previous episodes of severe hypoglycemia than the nonhypoglycemic group (0.92 plus-or-minus sign 1.18 vs. 0.25 plus-or-minus sign 0.68; P = .01). In only 64% of the episodes, an unusual circumstance such as strenuous physical activity or missed or delayed meals preceded the event. Multivariate analysis of the data by logistic regression showed risks of developing hypoglycemia of 2.5 per 0.5 U/day insulin and of 2.0 per previous episode of severe hypoglycemia. We conclude that severe hypoglycemia may be a recurrent problem in some diabetic children, but it does not appear to be related to age or blood glucose control. The presence of previous episodes may be a guide to identify patients at greater risk of developing severe hypoglycemia. Adherence to regular testing, strict spacing and consistency of meals, and extra food for extra activity may reduce this serious complication.

Side Effects of Drugs Annual-13,381 Side Effects of Drugs Annual-14,372

3/AB/4 (Item 4 from file: 70)
DIALOG(R)File 70:SEDBASE

00590742 SEDBASE No.: 00271777 Line Count: 104
Number of Cited Reference: 2
Drug Name: INSULIN HUMAN

Drug Classification: 44.01
Effect Interaction Name: CONSCIOUSNESS LOSS (SYMPTOM OF HYPOGLYCEMIA)
Effect Classification Code: 14.02
Synonym(s) for Effect Name: UNCONSCIOUSNESS
Source: Side Effects of Drugs Annual-13,381 Side Effects of Drugs Annual-14,372

EMBASE Abstract: The case-histories of 3 patients with insulin-dependent diabetes mellitus (IDDM) suggested that, after a switch from beef/porcine to human insulin, a given level of hypoglycaemia may cause less pronounced sympathoadrenal symptoms (tremor, sweating, &c), so that there is less warning of impending unconsciousness. This possibility was investigated by questioning of 176 IDDM patients who had switched from beef/porcine to human insulin with negligible change in dosage 1-48 months earlier. 66 (36%) said that their symptoms of hypoglycaemia had changed from those of

insulin doses at the time of the episode (U midline dot kg-1 midline dot day-1) were significantly higher than those of the nonhypoglycemic group (mean plus-or-minus sign SD 1.01 plus-or-minus sign 0.30 vs 0.89 plus-or-minus sign 0.29; P = 0.4). The hypoglycemic group had a significantly higher mean number of previous episodes of severe hypoglycemia than the nonhypoglycemic group (0.92 plus-or-minus sign 1.18 vs. 0.25 plus-or-minus sign 0.68; P = .01). In only 64% of the episodes, an unusual circumstance such as strenuous physical activity or missed or delayed meals preceded the event. Multivariate analysis of the data by logistic regression showed risks of developing hypoglycemia of 2.5 per 0.5 U/day insulin and of 2.0 per previous episode of severe hypoglycemia. We conclude that severe hypoglycemia may be a recurrent problem in some diabetic children, but it does not appear to be related to age or blood glucose control. The presence of previous episodes may be a guide to identify patients at greater risk of developing severe hypoglycemia. Adherence to regular testing, strict spacing and consistency of meals, and extra food for extra activity may reduce this serious complication.

Side Effects of Drugs Annual-13,381 Side Effects of Drugs Annual-14,372

3/AB/6 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

02357211 EMBASE No: 1983182215
Insulin antibody determination: Theoretical and practical considerations
Reeves W.G.
Dep. Immunol., Univ. Hosp., Nottingham NG7 2UH United Kingdom
Diabetologia (DIABETOLOGIA) (Germany) 1983, 24/6 (399-403)
CODEN: DBTGA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

The immunogenicity of insulin preparations is of both academic and clinical interest. The links between insulin antibodies and insulin allergy, some forms of insulin resistance and injection site lipoatrophy are well-established, but other more subtle metabolic effects require further examination. Contamination with impurities (e.g. proinsulin) has been a major factor in the immunogenicity of conventional bovine insulin preparations but the less frequent, although still detectable, immunogenicity of highly purified porcine and human preparations ramains enigmatic. Further work is required to analyse the physico-chemical factors involved, while the genetic control of the immune response to insulin is of fundamental interest. In order to facilitate comparative studies of different insulin preparations and data translation between different laboratories, it is essential that efforts be made to introduce some elements of standardisation in assay techniques, reporting of results and assessment of precision, accuracy and sensitivity. International collaborative laboratory studies have been successful in various other areas of clinical research relevant to diabetes, notably the series of HLA workshops and comparisons of the radioimmunoassay and bioassay of insulin and the radioimmunoassay of C - peptide . It is hoped that present efforts to achieve successful collaboration for insulin antibody determination will harmonise the diverse approaches to the problems which continue to surround the immunogenicity of insulin .

3/AB/7 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

00028834 EMBASE No: 1974018863
Studies on the conversion of proinsulin to insulin. III. Studies in vitro with a crude secretion granule fraction isolated from rat islets of Langerhans
Kemmler W.; Steiner D.F.; Borg J.
Dept. Biochem., Pritzker Sch. Med., Univ. Chicago, Ill. 60637 United States
Journal of Biological Chemistry (J. BIOL. CHEM.) 1973, 248/13 (4544-4551)
CODEN: JBCHA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Proinsulin is converted to insulin in an impure secretion granule fraction prepared from rat islets of Langerhans that have been labeled before homogenization with (sup 3H)leucine or (sup 3H)arginine. During incubation of this particulate fraction at pH 6.3 and 37degree, the initial rate of conversion of the endogenous labeled proinsulin is similar to that observed in whole islets, while externally added labeled proinsulin is not cleaved. Only intact granules catalyze conversion, and thus the pH optimum of about 6.0 for this process corresponds closely to that for granule stability. The most rapid in vitro cleavage of endogenous proinsulin is observed when the islets have been prelabeled with (sup 3H)leucine for 30 min, followed by a 15 min 'chase' to allow time for the transport of newly synthesized proinsulin to the Golgi apparatus and new secretory granules. Several proteinase inhibitors, including soybean trypsin inhibitor, pancreatic trypsin inhibitor, diisopropyl fluorophosphate, N alpha p tosyl L lysine chloromethyl ketone HCl, benzamidine, p nitrophenyl p' guanidinobenzoate HCl, N ethylmaleimide, and iodoacetate, do not inhibit conversion in vitro, possibly due to a lack of permeability of the granules to some of these substances; high concentrations of p chloromercuribenzoate completely inhibit conversion. The products of in vitro conversion have been characterized by polyacrylamide gel and thin layer electrophoresis as rat insulins I and II and their corresponding C peptides . The residual proinsulin fraction after incubation consists mainly of partly cleaved intermediate forms. When islets are prelabeled with (sup 3H)arginine before preparation of the granule fraction, in vitro conversion is accompanied by the release from the cleavage regions of free arginine rather than dipeptides of arginine or lysylarginine. Granule preparations disrupted by repeated freeze thawing lose their ability to introduce cleavages in intact proinsulin but are still able to rapidly remove COOH terminal arginine residues from lightly trypsinized proinsulin. A low level of tryptic like activity, as indicated by the slow cleavage of N alpha tosyl L (methyl sup 3H)arginine methyl ester, can still be detected in the disrupted preparations. These results are in accord with the hypothesis that enzyme(s) having trypsin like and carboxypeptidase B like activity exist in the secretory granules of the beta cells and participate in the conversion of proinsulin to insulin .

3/AB/8 (Item 1 from file: 345)
DIALOG(R)File 345:Inpadoc/Fam.& Legal Stat

16806979
Basic Patent (No,Kind,Date): DE 19951684 A1 20010503 <No. of Patents: 005>
NEUER IMMUNOLOGISCHER ASSAY ZUR BESTIMMUNG VON C-PEPTIDHALTIGEN KONTAMINANTEN IN PROBEN VON HUMANISULIN UND DESSEN DERIVATEN (German)
Patent Assignee: AVENTIS PHARMA GMBH (DE)
Author (Inventor): GERL MARTIN (DE); STEINERT CORNELIA (DE)
IPC: *G01N-033/536;

Derwent WPI Acc No: C 01-301419
Language of Document: German
Patent Family:

Patent No	Kind	Date	Applic No	Kind	Date	
AU 200112753	A5	20010508	AU 200112753	A	20001025	
DE 19951684	A1	20010503	DE 19951684	A	19991027	(BASIC)
EP 1228374	A2	20020807	EP 2000974449	A	20001025	
WO 200131336	A2	20010503	WO 2000EP10482	A	20001025	
WO 200131336	A3	20011108	WO 2000EP10482	A	20001025	

Priority Data (No,Kind,Date):
DE 19951684 A 19991027
WO 2000EP10482 W 20001025

3/AB/9 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0010376 DBR Accession No.: 83-03079
Purification of porcine proinsulin by high-performance liquid chromatography - detection of trace contaminants causing antigeniity in therapeutic insulin preparations
AUTHOR: Parman A U; Rideout J M
CORPORATE SOURCE: Division of Clinical Chemistry, M.R.C. Clinical Research Centre, Harrow, Middlesex HA1 3UJ, Great Britain.
JOURNAL: J.Chromatogr. (256, 2, 283-91) 1983
CODEN: JOCRAM
LANGUAGE: English
ABSTRACT: A procedure has been developed for the purification of pig proinsulin by HPLC from a preparation obtained as a side product during the Sephadex G-50 gel filtration of an impure pig insulin preparation. The apparatus used was a Varian 5000 liquid chromatograph with computerized gradient making facility, Varian UV 50 variable wavelength detector and an ODS-C18 olumn. The crude preparation separated into 5 different groups of proteins and the proinsulin-containing peak was identified. The peak fraction was purified by separation, pooling, freeze-drying, desalting, reprecipitation and drying before HPLC chromatography as a final purification step. Proinsulin is a useful antigen for raising species-specific antibodies binding C - peptide . Insulin and proinslulin preparations may be contaminated with spontaneous conversion products, which can be detected better with a gradient system of HPLC. This is important in view of the potential antigenicity of therapeutic preparations which has been attributed to traces of contaminants. (9 ref)
?ds

Set	Items	Description
S1	25619	(C(W)PEPTIDE? OR C(W)PROTEIN? OR PREPROINSULIN?) (S) INSULIN?
S2	9	S1 AND IMPUR?
S3	9	RD (unique items)
S4	16176	S1 AND (ASSAY? OR ANAL? OR TEST? OR EXAM? OR EVAL?)
S5	1834	S4 (S) (ANTIBOD? OR AB OR MAB OR PAB)
S6	746	RD (unique items)
S7	61	S6 AND (TRACER? OR LABEL?)
S8	1	S7 AND (NON(W)RADIO?)
S9	10938655	8 NOT S3
S10	1	S8 NOT S3

?t10/7/1

10/7/1 (Item 1 from file: 351)

DIALOG(R)File 351:Derwent WPI

013817207
WPI Acc No: 2001-301419/200132
Assay for detecting C-peptide contamination in recombinant human insulin, useful for quality control, comprises measuring luminescence of labeled C-peptide tracer in immunoassay
Patent Assignee: AVENTIS PHARMA DEUT GMBH (AVET)
Inventor: GERL M; STEINERT C
Number of Countries: 094 Number of Patents: 004
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
DE 19951684	A1	20010503	DE 1051684	A	19991027	200132	B
WO 200131336	A2	20010503	WO 2000EP10482	A	20001025	200132	
AU 200112753	A	20010508	AU 2Q0112753	A	20001025	200149	
EP 1228374	A2	20020807	EP 2000974449	A	20001025	200259	
			WO 2000EP10482	A	20001025		

Priority Applications (No Type Date): DE 1051684 A 19991027
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
DE 19951684	A1		33	G01N-033/536	
WO 200131336	A2	E		G01N-033/53	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

AU 200112753	A		G01N-033/53	Based on patent WO 200131336
EP 1228374	A2	E	G01N-033/74	Based on patent WO 200131336

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

Abstract (Basic): DE 19951684 A1

NOVELTY - Non - radioactive assay for examining recombinant human insulin (I) or its derivatives comprises measuring luminescence of labeled C-peptide tracer in immunoassay.

DETAILED DESCRIPTION - Non - radioactive assay for examining recombinant human insulin (I) or its derivatives (produced by enzymatic cleavage of a precursor) for presence of preproinsulin , or its derivatives, insulin derivatives that contain C - peptide and/or isolated C - peptide comprises mixing the test sample with diluting buffer, then treating sequentially with a tracer , an antibody and a ' C - peptide second antibody bead'. The resulting mixture analyzed in a luminometer.

USE - To determine contamination of human insulin (including variants with amino acid alterations) by immunoreactive C-peptide components, i.e. for quality control.

ADVANTAGE - The method is very sensitive (detection limit for C-peptide 0.4 ng/ml), precise and reproducible. It eliminates the need for radioactive labels ; uses a very stable tracer ; requires only about 5 hr; involves no washing steps and can be used to analyze 50 samples per day. The procedure is simple and inexpensive (about DM 150 per assay); does not require pH adjustment and is applicable to different forms of recombinant insulin.

pp; 33 DwgNo 0/9

Derwent Class: B04; D16; S03
International Patent Class (Main): G01N-033/53; G01N-033/536; G01N-033/74
?

sympathoadrenal activation to those of neuroglycopenia. This disadvantage of human insulin is an argument for continued availability of beef/porcine insulin.

EMBASE Abstract: The incidence of severed hypoglycemia was determined in a 1-yr prospective study of 350 insulin-dependent diabetic (IDDM) children. There were no significant differences in mean glycosylated hemoglobin, age, and duration of disease between the patients who had severe hypoglycemia and those who did not. There were 25 episodes in 24 patients (6.8%). Their insulin doses at the time of the episode (U midline dot kg-1 midline dot day-1) were significantly higher than those of the nonhypoglycemic group (mean plus-or-minus sign SD 1.01 plus-or-minus sign 0.30 vs 0.89 plus-or-minus sign 0.29; P = 0.4). The hypoglycemic group had a significantly higher mean number of previous episodes of severe hypoglycemia than the nonhypoglycemic group (0.92 plus-or-minus sign 1.18 vs. 0.25 plus-or-minus sign 0.68; P = .01). In only 64% of the episodes, an unusual circumstance such as strenuous physical activity or missed or delayed meals preceded the event. Multivariate analysis of the data by logistic regression showed risks of developing hypoglycemia of 2.5 per 0.5 U/day insulin and of 2.0 per previous episode of severe hypoglycemia. We conclude that severe hypoglycemia may be a recurrent problem in some diabetic children, but it does not appear to be related to age or blood glucose control. The presence of previous episodes may be a guide to identify patients at greater risk of developing severe hypoglycemia. Adherence to regular testing, strict spacing and consistency of meals, and extra food for extra activity may reduce this serious complication.

Side Effects of Drugs Annual-13,381 Side Effects of Drugs Annual-14,372

3/AB/5 (Item 5 from file: 70)
DIALOG(R)File 70:SEDBASE

00590732 SEDBASE No.: 00271755 Line Count: 104
Number of Cited Reference: 2
Drug Name: INSULIN HUMAN

Drug Classification: 44.01
Effect Interaction Name: CONSCIOUSNESS LOSS (SYMPTOM OF HYPOGLYCEMIA)
Effect Classification Code: 14.02
Synonym(s) for Effect Name: UNCONSCIOUSNESS
Source: Side Effects of Drugs Annual-13,381 Side Effects of Drugs Annual-14,372

EMBASE Abstract: The case-histories of 3 patients with insulin-dependent diabetes mellitus (IDDM) suggested that, after a switch from beef/porcine to human insulin, a given level of hypoglycaemia may cause less pronounced sympathoadrenal symptoms (tremor, sweating, &c), so that there is less warning of impending unconsciousness. This possibility was investigated by questioning of 176 IDDM patients who had switched from beef/porcine to human insulin with negligible change in dosage 1-48 months earlier. 66 (36%) said that their symptoms of hypoglycaemia had changed from those of sympathoadrenal activation to those of neuroglycopenia. This disadvantage of human insulin is an argument for continued availability of beef/porcine insulin.

EMBASE Abstract: The incidence of severed hypoglycemia was determined in a 1-yr prospective study of 350 insulin-dependent diabetic (IDDM) children. There were no significant differences in mean glycosylated hemoglobin, age, and duration of disease between the patients who had severe hypoglycemia and those who did not. There were 25 episodes in 24 patients (6.8%). Their